Please amend the above-referenced application as follows:

IN THE CLAIMS

Please cancel claims 24, 25, 35, 36-38.

Please amend the following claims.

18. (Amended) An apparatus for monitoring the formation of a nucleic acid amplification reaction product in real time, the apparatus comprising:

a sample holder for holding a sample of nucleic acids to be amplified;

a fiber optic cable for illuminating a volume of the sample with an excitation beam;

a lens co-axially disposed with the fiber optic cable for focusing the excitation beam into the volume of the sample [, the lens] and for collecting from the sample and transmitting to the fiber optic cable a first fluorescent signal whose intensity is proportional to the concentration of the amplification reaction product [in the volume of sample illuminated by the excitation beam] and a second fluorescent signal whose intensity is proportional to the volume of the sample illuminated by the excitation beam; and

a detection and analysis mechanism for receiving the first and second fluorescent signals from the fiber optic cable at a plurality of times, the detection and analysis mechanism measuring the intensities of the first and second fluorescent signals at the plurality of times and producing a plurality of corrected intensity signals, each corrected intensity signal corresponding to a ratio between the intensities of the first and second fluorescent signals at a given time.

19. (Amended) The apparatus according to claim 18 wherein [the first and second fluorescent signals each have an intensity and] the detection and analysis mechanism provides a readout [including a ratio between the intensity of the first fluorescent signal and the intensity of the second fluorescent signal] corresponding to the plurality of corrected intensity signals as a function of time.

17. (Amended) The apparatus according to claim [15] 16 wherein the removable reaction chamber is sealable.

26. 13 (Amended) The method according to claim [24] ~~39~~ 12 wherein the first fluorescent indicator is a complex-forming dye.

C3

27. 14 (Amended) The method according to claim [24] ~~39~~ 12, further including the step of sealing the sample within the sample holder prior to transmitting an excitation beam into the sample holder.

28. 15 (Amended) The method according to claim [24] ~~39~~ 12 wherein the sample holder includes an optical interface through which the excitation beam is transmitted [from the lens] to the sample, the sample holder also including an air gap separating the optical interface from the sample, the method further including the step of heating the optical interface to prevent condensation of the sample on the optical interface.

C4

30. 17 (Amended) The method according to claim [24] ~~39~~ 12 wherein the step of [adding a sample to] taking a sample holder includes

adding a sample to a reaction chamber which is removable from the sample holder; and

adding the removable reaction chamber to the sample holder.

C5

33. (Amended) The method according to claim [24] 39 wherein [the nucleic acid amplification reaction is] performing at least one amplification includes performing at least one cycle of a polymerase chain reaction.

34. (Amended) The method according to claim [24] 39 wherein [the nucleic acid amplification reaction is] performing at least one amplification includes performing at least one cycle of a ligase chain reaction.

Please add the following new claims --

C6

39. A method for monitoring the formation of a nucleic acid amplification reaction product in real time comprising:

taking a sample holder containing a nucleic acid sequence to be amplified to form a nucleic acid amplification reaction product, a first fluorescent indicator which produces a first fluorescent signal when illuminated by an excitation beam whose intensity is proportional to a

concentration of the amplification reaction product in the sample, and a second fluorescent indicator which produces a second fluorescent signal when illuminated by the excitation beam whose intensity is proportional to a volume of sample illuminated by the excitation beam;

transmitting an excitation beam into the sample holder and measuring the intensities of the first and second fluorescent signals;

performing at least one amplification of the nucleic acid sequence in the sample holder;

transmitting an excitation beam into the sample holder after the amplification and measuring the intensities of the first and second fluorescent signals; and

monitoring the formation of the nucleic acid amplification reaction product in real time by calculating a corrected intensity signal corresponding to a ratio between the intensity of the first and second fluorescent signals at a given time before and after amplifying the nucleic acid sequence, a change in the corrected intensity signal after amplification indicating the formation of the nucleic acid amplification reaction product.

40. A method for monitoring the formation of multiple nucleic acid amplification reaction products in real time comprising:

taking multiple sample holders, each sample holder containing a nucleic acid sequence to be amplified to form a nucleic acid amplification reaction product, a first fluorescent indicator which produces a first fluorescent signal when illuminated by an excitation beam whose intensity is proportional to a concentration of the amplification reaction product in the sample, and a second fluorescent indicator which produces a second fluorescent signal when illuminated by the excitation beam whose intensity is proportional to a volume of sample illuminated by the excitation beam;

transmitting an excitation beam into the multiple sample holders and measuring the intensities of the first and second fluorescent signals;

performing at least one amplification of the nucleic acid sequences in the multiple sample holders;

transmitting an excitation beam into the multiple sample holders after the amplification and measuring the intensities of the first and second fluorescent signals; and

monitoring the formation of nucleic acid amplification reaction products in the multiple sample holders in real time by calculating corrected intensity signals before and after amplifying the nucleic acid sequences in the multiple sample holders, each corrected intensity

signal corresponding to a ratio between the intensity of the first and second fluorescent signals at a given time, a change in the corrected intensity signal after amplification indicating the formation of the nucleic acid amplification reaction product.

41. A method for monitoring the formation of multiple nucleic acid amplification reaction products in real time comprising:

taking a sample holder containing a plurality of nucleic acid sequences to be amplified to form a plurality of nucleic acid amplification reaction products, a plurality of first fluorescent indicators which produce a first fluorescent signal when illuminated by an excitation beam whose intensity is proportional to a concentration of the amplification reaction product in the sample, and a second fluorescent indicator which produces a second fluorescent signal when illuminated by the excitation beam whose intensity is proportional to a volume of sample illuminated by the excitation beam;

transmitting an excitation beam into the sample holder and measuring the intensities of the first and second fluorescent signals;

performing at least one amplification of the nucleic acid sequences in the sample holder;

transmitting an excitation beam into the sample holder after the amplification and measuring the intensities of the first and second fluorescent signals; and

monitoring the formation of the plurality of nucleic acid amplification reaction products in the sample holder in real time by calculating corrected intensity signals before and after amplification for each of the plurality of nucleic acid sequences in the sample holder, each corrected intensity signal corresponding to a ratio between the intensity of the first and second fluorescent signals at a given time, a change in the corrected intensity signal after amplification indicating the formation of the nucleic acid amplification reaction product.

42. A method for monitoring the formation of a nucleic acid amplification reaction product in real time comprising:

taking a sample holder containing a nucleic acid sequence to be amplified to form a nucleic acid amplification reaction product, and first and second fluorescent indicators covalently attached to an oligonucleotide capable of hybridizing to the amplification reaction product, the first fluorescent indicator producing a first fluorescent signal when illuminated by the excitation beam whose intensity is proportional to the concentration of amplification

reaction product in the sample, the second fluorescent indicator producing a second fluorescent signal when illuminated by the excitation beam whose intensity is proportional to the volume of the sample illuminated by the excitation beam, the second fluorescent indicator also quenching the fluorescence of the first fluorescent indicator;

transmitting an excitation beam into the sample holder and measuring the intensities of the first and second fluorescent signals;

performing at least one amplification of the nucleic acid sequence in the sample holder;

transmitting an excitation beam into the sample holder after the amplification and measuring the intensities of the first and second fluorescent signals; and

monitoring the formation of the nucleic acid amplification reaction product in real time by calculating a corrected intensity signal corresponding to a ratio between the intensity of the first and second fluorescent signals at a given time before and after amplifying the nucleic acid sequence, a change in the corrected intensity signal after amplification indicating the formation of the nucleic acid amplification reaction product. --.

REMARKS

This Amendment is in response to the Examiner's Final Office Action mailed July 2, 1996 (Paper No. 14). Claims 13-38 were reviewed by the Examiner. Applicants presently cancel claims 24, 25, 35, 36-38, add new claims 39-42, and amend claims 13, 14 17, 26, 28, 30 and 33-34. Now pending are claims 13-23, 26-34, and 39-42.

With regard to the new claims, new claim 39 corresponds to claim 24 rewritten. New claim 40 corresponds to claim 36 rewritten. New claim 41 corresponds to claim 38 rewritten. New claim 42 corresponds to claim 35 rewritten in independent form.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. Rejection Of Claims 17 and 24-38 Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 17 and 24-38 under 35 U.S.C. § 112, second paragraph for indefiniteness. Applicants presently amend claims 17, 24 (now claim 39), 25, 36 (now claim 40) and 38 (now claim 41) in order to address the Examiner's rejection. Applicants